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Prediction of Extensive Myocardial Fibrosis in Nonhigh Risk Patients With Hypertrophic Cardiomyopathy

D.H. Frank Gommans, MD[a,*], G. Etienne Cramer, MD[a], Michael A. Fouraux, PhD[b], Jeannette Bakker, MD, PhD[c], Michelle Michels, MD, PhD[d], Hendrik-Jan Dieker, MD, PhD[a], Janneke Timmermans, MD[a], Carlo L.M. Marcelis, MD[e], Freek W.A. Verheugt, MD, PhD[a], Menko-Jan de Boer, MD, PhD[a], Marcel J.M. Kofflard, MD, PhD[f], Rudolf A. de Boer, MD, PhD[g], and Marc A. Brouwer, MD, PhD[a]

In nonhigh risk patients with hypertrophic cardiomyopathy (HC), the presence of extensive late gadolinium enhancement (LGE_{ext}) at cardiovascular magnetic resonance (CMR) imaging has been proposed as a risk modifier in the decision process for implantable cardioverter defibrillator implantation. With a pretest risk of about 10%, a strategy that alters the likelihood of LGE_{ext} could markedly affect efficacious CMR imaging. Our aim was to study the potential of clinical variables and biomarkers to predict LGE_{ext}. In 98 HC patients without any clear indication for implantable cardioverter defibrillator implantation, we determined the discriminative values of a set of clinical variables and a panel of biomarkers (hs-cTnT, NTproBNP, GDF-15, and Gal-3, CICP) for LGE_{ext}, that is, LGE ≥15% of the left ventricular mass. LGE_{ext} was present in 10% (10/98) of patients. The clinical prediction model contained a history of nonsustained ventricular tachycardia, maximal wall thickness and reduced systolic function (c-statistic: 0.868, p <0.001). Of all biomarkers, only hs-cTnT was associated with LGE_{ext}, in addition to the improved clinical model of diagnostic accuracy (p = 0.04). A biomarker-only strategy allowed the exclusion of LGE_{ext} in half of the cohort, in case of a hs-cTnT concentration less than the optimal cutoff (Youden index; 8 ng/L—sensitivity 100%, specificity 54%). In conclusion, in this nonhigh risk HC cohort, the pretest likelihood of LGE_{ext} can be altered using clinical variables and the addition of hs-cTnT. The promising findings with the use of hs-cTnT only call for new initiatives to study its impact on efficacious CMR imaging in a larger HC population, either with or without additional use of clinical variables. **(Am J Cardiol 2018;122:483–489)**

Hypertrophic cardiomyopathy (HC) is a major cause of sudden cardiac death (SCD) with an incidence of <1% per year, which poses a major clinical challenge for its prediction.[1,2] Importantly, the highest absolute number of SCDs still occur in the large group of nonhigh risk HC patients without a clear indication for an implantable cardioverter defibrillator.[1–4] Recently, clinical experts have suggested to incorporate extensive late gadolinium enhancement (LGE) in clinical decision making for this category of HC patients.[5] As extensive LGE (≥15% of left ventricular [LV] mass) is only seen in about 10%,[6] a strategy based on easily obtainable characteristics that would alter the pretest likelihood, would be a more cost-effective approach than routine LGE cardiovascular magnetic resonance (CMR) imaging.[7,8] In addition to various clinical variables (e.g., LV mass, wall thickness, and nonsustained ventricular tachycardia [NSVT][9–11]) biomarkers like cardiac troponin, natriuretic peptides, and markers of collagen turnover have repeatedly been associated with LGE in HC.[12–19] In the previously mentioned clinical context, we aimed to identify predictors of extensive LGE between routinely assessed clinical variables and a broad panel of biomarkers in nonhigh risk HC patients. In addition, we demonstrate the predictive value of the addition of biomarkers in comparison to a prediction model with clinical variables only.

Methods

For this analysis, we selected nonhigh risk patients from a large cohort of HC patients who participated in a Dutch multicenter study on CMR imaging and biomarkers.[20] In short, adult HC patients from different hospitals were enrolled at 2 outpatient clinics (Radboud University Medical Center, Nijmegen and Albert Schweitzer Hospital, Dordrecht, The Netherlands) from 2008 to 2014. Patients had to fulfill the diagnostic criteria for HC according to the prevailing guidelines at the time of inclusion and should not

[a]Department of Cardiology, Radboud University Medical Center, Nijmegen, Gelderland, The Netherlands; [b]Department of Clinical Chemistry, Albert Schweitzer Hospital, Dordrecht, The Netherlands; [c]Albert Schweitzer Hospital, Department of Radiology, Dordrecht, The Netherlands; [d]Department of Cardiology, Erasmus Medical Center, Rotterdam, South Holland, The Netherlands; [e]Department of Clinical Genetics, Radboud University Medical Center, Nijmegen, Gelderland, The Netherlands; [f]Department of Cardiology, Albert Schweitzer Hospital, Dordrecht, The Netherlands; and [g]Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands. Manuscript received January 21, 2018; revised manuscript received and accepted April 13, 2018.

See page 488 for disclosure information.

*Corresponding author: Tel: +31-24-3616785; fax: +31-24-3540800.
E-mail address: frank.gommans@radboudumc.nl (D.H.F. Gommans).

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have a history of coronary artery disease or septal reduction therapy. For this analysis, data on the extent of LGE had to be available. Furthermore, we selected HC patients who are considered not to be at high SCD risk based on the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines (i.e., low to intermediate risk HC patients). Accordingly, we excluded patients with a family history of SCD, extreme hypertrophy (≥30 mm) or a recent unexplained syncope (i.e., patients in whom ICD implantation is considered reasonable according to the latest AHA/ACC guidelines).[2] The study complies with the Declaration of Helsinki and the protocol was approved by the local ethical committees and conducted accordingly. All participants provided written informed consent.

CMR imaging was performed on 1.5 T CMR systems (Philips Achieva [Philips Healthcare, Best, The Netherlands] or Siemens Avanto [Siemens Health Care, Erlangen, Germany]) according to local imaging protocols, as previously described in more detail.[20] T1-weighted inversion-recovery imaging was performed to assess LGE 10 minutes after the administration of 0.2 mmol/kg contrast medium (Dotarem; Guerbet, Gorinchem, The Netherlands).

Images were analyzed with commercially available software (QMass 7.5, Medis, Leiden, The Netherlands) by three observers (FG, JB, and HD) unaware of the subjects' clinical information. The extent of LGE was scored visually according to a semi-quantitative score, previously validated in HC.[21] The definition of extensive LGE was met in case the LGE extent comprised ≥15% of the LV mass.

Blood samples were obtained by trained personnel and processed within 60 minutes after phlebotomy, and stored at −80°C until further analysis. Serum samples were used for the determination of the biomarkers (1) cardiac troponin T using the highly sensitive assay (hs-cTnT), (2) N-terminal-pro-B-type-natriuretic peptide (NTproBNP), (3) Galectin-3 (Gal-3), (4) soluble tumorigenicity suppressor2 (sST2), (5) growth differentiation factor-15 (GDF-15), and (6) C-terminal propeptide of type I collagen (CICP). Variability and performance in healthy controls and patients with heart failure have been published.[22] We refer to Appendix A for a detailed description of the assays.

Continuous variables are presented as means (±standard deviations) or medians (interquartile ranges) and were compared between patients with and without extensive LGE using a Student's t or Mann−Whitney U test, whichever is appropriate. Dichotomous variables were compared using a chi-square or Fisher's exact test, whichever appropriate. A p value of <0.05 was considered significant (two-sided). Then, multivariable regression analysis was performed. A stepwise forward approach was adopted to predict extensive LGE based on the likelihood-ratio-test (P-in, 0.05; P-out, 0.10). First, we constructed a model for prediction of extensive LGE with the clinical variables that differed between patients with and without extensive LGE ($p<0.10$; model 1). Second, we constructed model 2 for prediction of extensive LGE with the addition of the biomarkers that differed between patients with and without extensive LGE ($p<0.10$). To assess the calibration of the models, we used the Hosmer−Lemeshow goodness-of-fit statistical method. Receiver operating characteristic (ROC) analysis using c-statistics was performed to determine the area under the curve of both models, and of each biomarker variable included in model 2 separately. The cut-off value for the continuous variables was determined using the Youden index. Statistical analysis was performed with IBM SPSS Statistics 22 (IBM Corp, Armonk, New York).

Results

For the present analysis, 98 nonhigh HC patients selected from our total HC cohort of 141 HC patients were studied (61% male, age 55 ± 14 years) (Figure 1 and Table 1).[20] Most patients were a- or mildly symptomatic with 96 (98%) in New York Heart Association class I to II. The presence of LGE was demonstrated in 56 (57%) patients. In these 56 patients, the extent of LGE comprised 8% (interquartile ranges 3 to 13%) of the LV mass. In 10 (10%) patients the extent of LGE was ≥15%.

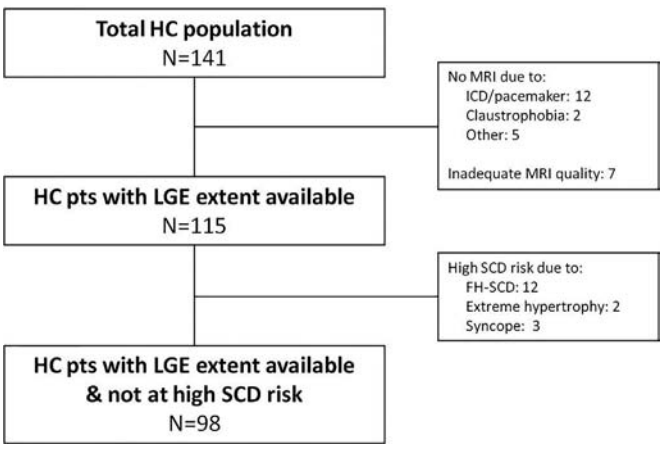

Figure 1. Flow chart of our HC study population.

Our total HC population comprised 141 HC patients. Twenty-six HC patients were excluded because there was no data available on LGE extent. Seventeen HC patients were excluded because they were considered to be at high SCD risk according to the ACC/AHA guidelines, in which an ICD implantation is considered reasonable.

ACC = American college of cardiology; AHA = American heart association; FH-SCD = family history of sudden cardiac death; HC = hypertrophic cardiomyopathy; ICD = implantable cardioverter defibrillator; LGE = late gadolinium enhancement; MRI = magnetic resonance imaging; SCD = sudden cardiac death.

Table 1
Baseline characteristics stratified according to extensive late gadolinium enhancement

Variable	Total (n = 98)	LGE extent		p value
		<15% (n = 88)	≥15% (n = 10)	
Age at participation (years)	55 ± 14	55 ± 15	57 ± 12	0.74
Men	60 (61%)	53 (60%)	7 (70%)	0.74
Age at diagnosis (years)*	49 ± 16	50 ± 16	40 ± 16	0.09
Pathogenic mutation present	46 (53%)	39 (50%)	7 (78%)	0.16
Atrial fibrillation*	18 (18%)	14 (16%)	4 (40%)	0.08
Hypertension	40 (41%)	35 (40%)	5 (50%)	0.74
Current smoker	15 (15%)	14 (16%)	1 (10%)	1.0
Dyslipidemia†	29 (30%)	24 (27%)	5 (50%)	0.16
Diabetes mellitus	5 (5%)	4 (5%)	1 (10%)	0.42
Creatinine (μmol/l)	84 ± 16	84 ± 16	89 ± 20	0.37
Systolic blood pressure (mm Hg)	131 ± 22	131 ± 22	133 ± 20	0.76
Heart rate (beats/minute)	73 ± 12	73 ± 12	76 ± 15	0.36
Framingham 10-year heart risk (%)	15 (5-26)	15 (5-25)	23 (7-31)	0.37
Risk factors for SCD				
History of nonsustained VT*	14 (15%)	10 (12%)	4 (40%)	0.04
Abnormal BP response*	11 (12%)	8 (9%)	3 (30%)	0.09
Symptoms				
Chest pain	18 (18%)	18 (21%)	-	0.20
Dyspnea (NYHA class ≥II)	43 (44%)	40 (46%)	3 (30%)	0.51
Echocardiography				
Maximal LV wall thickness (mm)*	16 (13-19)	16 (13-19)	18 (16-21)	0.08
LVMI (g/m^2)*	125 (103-162)	124 (102-155)	160 (127-179)	0.05
Reduced LV systolic function*	8 (8%)	5 (6%)	3 (30%)	0.03
LV outflow tract gradient at rest ≥30 mm Hg	18 (19%)	18 (21%)	-	0.20
Left atrial diameter (mm)	44 (39-50)	44 (39-48)	45 (42-58)	0.26
Therapy				
Beta-blocker	50 (51%)	43 (49%)	7 (70%)	0.32
Calcium antagonist	12 (12%)	10 (11%)	2 (20%)	0.35

Data are presented as means ± standard deviations, medians (interquartile ranges) or numbers (percentages). BP = blood pressure; LGE = late gadolinium enhancement; LV = left ventricle; LVMI = left ventricle mass indexed to body surface area; NYHA = New York heart association; SCD = sudden cardiac death; VT = ventricular tachycardia.

* These variables were used for multivariate logistic regression analysis.

† Dyslipidemia was defined as a total cholesterol > 6.5 mmol/l.

Patients with extensive LGE tended to be younger at the time of diagnosis compared with patients without extensive LGE (Table 1). Atrial fibrillation tended to be more often present in patients with extensive LGE. A history of NSVTs was more often present in these patients. With regard to echocardiographic parameters, patients with extensive LGE had a higher LV mass indexed to BSA and had a numerically higher maximal LV wall thickness. Lastly, 3 of 10 patients with extensive LGE had a reduced LV systolic function compared with 5 of 88 patients without extensive LGE.

The median hs-cTnT concentration was twice as high in patients with extensive LGE (Table 2). No significant differences were observed for NTproBNP or any of the other biomarkers.

After multivariable regression analysis with the clinical variables, the clinical prediction model consisted of a

Table 2
Biomarkers stratified according to extensive late gadolinium enhancement

Biomarkers	Total (n = 98)	LGE extent		p value
		<15% (n = 88)	≥15% (n = 10)	
Hs-cTnT (ng/L)*	8 (4-14)	8 (3-13)	16 (11-27)	0.001
NTproBNP (ng/L)	120 (76-351)	120 (69-323)	238 (106-360)	0.30
sST2 (ng/mL)	25 (19-34)	25 (19-35)	22 (18-31)	0.71
GDF-15 (ng/L)	837 (515-1212)	837 (510-1181)	1007 (717-1352)	0.24
Gal-3 (ng/mL)	18 (14-20)	17 (14-20)	18 (13-20)	0.79
CICP (ng/mL)	126 (106-160)	126 (106-159)	126 (104-184)	0.69

Data are presented as means ± standard deviations or medians (interquartile ranges). LGE = late gadolinium enhancement.

* This variable was used for multivariate logistic regression analysis.

Table 3
Models 1 and 2 for prediction for extensive late gadolinium enhancement

Model 1: Routine clinical variables	Adjusted OR	95% CI	p value
History of non-sustained VT	6.80	1.32-35.20	0.022
Maximal LV wall thickness (mm)	1.23	1.03-1.48	0.023
Reduced LV systolic function	9.31	1.48-58.40	0.017
Model 2: Routine clinical variables + biomarkers	**Adjusted OR**	**95% CI**	**p value**
History of non-sustained VT	10.00	1.54-64.78	0.016
Maximal LV wall thickness (mm)	1.23	1.012-1.497	0.037
Reduced LV systolic function	9.57	1.33-68.86	0.025
Hs-cTnT (ng/L)	1.07	1.001-1.132	.046

CI = confidence interval; LGE = late gadolinium enhancement; LV = left ventricle; OR = odds ratio; VT = ventricular tachycardia.

history of NSVT, reduced LV systolic function and maximal echocardiographic LV wall thickness (model 1). As for model 2, addition of hs-cTnT significantly improved the model (difference in −2 log likelihood was 4.206, p = 0.04) (Table 3). The calibration of the two models was adequate (Hosmer−Lemeshow goodness-of-fit significance level, >0.05). For model 1, ROC analysis demonstrated a high discriminative ability (area under the curve, c-statistic: 0.868 [95% confidence interval [CI] 0.780 to 0.956, p <0.001]). For model 2, the discriminative ability was even slightly higher (area under the curve, c-statistic: 0.900 [95% CI 0.836 to 0.964], p <0.001) (Figure 2). As a single variable, none of the clinical characteristics (history of NSVT, abnormal LV function, and LV wall thickness) demonstrated valuable discriminative ability for prediction of extensive LGE (c-statistics, p = N.S.). In contrast, ROC analysis of hs-cTnT as a single variable demonstrated good discriminative value (area under the curve, c-statistic of 0.818 [95% CI 0.716 to 0.920], p = 0.001) (Figure 3). Based on the Youden index, the optimal cut-off value for hs-cTnT was 8 ng/L. Of note, this was also the median concentration of our cohort. Using this cutoff, the sensitivity and specificity of hs-cTnT for extensive LGE were 100% and 54%, respectively. Consequently, the negative and positive predictive values for extensive LGE were 100% and 19% in our population.

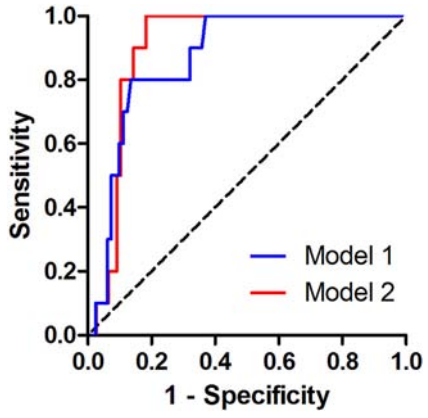

Figure 2. ROC curves for prediction of extensive LGE with clinical variables only (model 1) and with addition of hs-cTnT (model 2).
This figure demonstrates the discriminative ability for extensive LGE with clinical variables only (a history of NSVT, reduced LV systolic function and maximal LV wall thickness on echocardiography) (model 1: c-statistic: 0.868). Model 2 represents the discriminative ability with the addition of hs-cTnT (c-statistic: 0.900).
Hs-cTnT = cardiac troponin T assessed with a highly sensitive assay; LGE = late gadolinium enhancement.

Discussion

In an era of increasing interest in CMR imaging as part of the workup to assess whether nonhigh risk HC patients qualify for ICD implantation, we herein describe predictors of extensive LGE. We found that a set of three clinical variables had a high discriminative value, with a significant improvement in diagnostic accuracy after addition of hs-cTnT. Even without accounting for the history of NSVT, reduced LV systolic function, and maximal LV wall thickness on echocardiography, a strategy based on the use of hs-cTnT by itself showed remarkable results. Based on the optimal cutoff for hs-cTnT, extensive LGE could reliably be excluded in half of the cohort.

Previous reports have associated various clinical variables with the presence of LGE, such as a history of NSVT and measures of LV hypertrophy.[9–11] Moreover, maximal wall thickness on CMR imaging was reported to be independently predictive of the presence of LGE.[13] As the clinical importance of the mere presence of LGE is

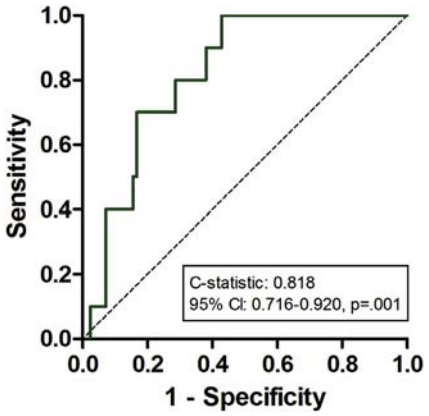

Figure 3. ROC curve of hs-cTnT for the prediction of extensive LGE.
This figure demonstrates the discriminative ability of hs-cTnT for extensive LGE in our cohort of low to intermediate risk HC patients.
Hs-cTnT = cardiac troponin T assessed with a highly sensitive assay; LGE = late gadolinium enhancement.

limited, we focused on the prediction of extensive LGE and only with variables available before CMR imaging. Our findings that a history of NSVT and a reduced LV systolic function on echocardiography were associated with extensive LGE corroborates with previous findings. Clearly, myocardial scar, which is suggested by the presence of extensive LGE, is a substrate for ventricular arrhythmias and leads to adverse remodeling.[11] The association between maximal LV wall thickness and extensive LGE corresponds with previous observations that HC patients with more hypertrophy more often have LGE.[9,10] This can most likely be explained by an increased myocardial oxygen demand and consequent ischemia with myocardial cell death.

Cardiac troponin, natriuretic peptides, and markers of collagen turnover have been associated with the presence of LGE in HC.[12−18] In addition, some studies addressed the predictive value of these biomarkers for the presence of LGE in HC.[12−14] Notably, a correlation was demonstrated between biomarker concentrations and the extent of LGE, although data are limited.[13−17,19]

The other biomarkers in our panel (Gal-3, sST2, and GDF-15) have been implicated in myocardial fibrosis, stress, and inflammation in heart failure. Gal-3 has been associated with LGE in nonischemic dilated cardiomyopathy patients, but in HC this association could not be confirmed.[23−25] Regarding sST2 in relation to LGE CMR imaging, only two reports in HC are available, of which one suggested an association with LGE extent.[25,26] To our knowledge, we are the first to describe GDF-15 in relation to LGE CMR imaging in HC.[27−29]

With regard to our results, the observed association between hs-cTnT and extensive LGE corroborates with previous studies and can be explained by both hs-cTnT and LGE being markers of myocyte injury.[12,13,15,18] Concerning NTproBNP, we did not observe a difference between HC patients with or without extensive LGE, despite a difference in systolic function among groups. Possibly, the absence of a difference in NTproBNP may be related to the inclusion of a nonhigh risk HC population with, in general, low biomarker concentrations and a low incidence of extensive LGE limiting the statistical power. As for concentrations of CICP and the more novel markers (sST2, GDF-15, and Galectin-3), we did not observe differences in relation to extensive LGE. This observation may be explained by the hypothesis that the systemic concentrations of these markers are only partly or indirectly reflective of myocardial fibrosis present in the LV myocardium.[12,30] To further assess the potential for these markers, larger studies are warranted.[24] Notwithstanding our modest sample size, our current results put hs-cTnT forward as the most promising biomarker for prediction of extensive LGE in nonhigh risk HC patients.

Based on a recent meta-analysis, clinical experts have suggested the use of extensive LGE as a SCD risk modifier for nonhigh risk HC patients.[19] The prevalence of extensive LGE can roughly be estimated at about 10% in these patients and implies an approximately twofold higher risk of SCD and the consideration of ICD implantation.[5,6] Notably, the majority of HC patients is at nonhigh SCD risk and only 1 of 10 would demonstrate extensive LGE on CMR imaging. In this context, it has recently been hypothesized that biomarkers, and hs-cTnT in particular, may be used as a "gateway" to perform LGE CMR imaging.[7,8] A strategy based on easily obtainable characteristics that would alter the pretest likelihood of extensive LGE before CMR imaging would increase efficacious use of LGE CMR imaging for SCD risk stratification in HC.[7,8] This may especially be valuable for institutions with limited resources to perform CMR imaging.

In our cohort, we demonstrated that extensive LGE can be predicted with a high discriminatory ability with a set of clinical variables. Importantly, the addition of hs-cTnT not only improved prediction, but the use of hs-cTnT by itself yielded a high discriminatory ability that approximates that of the set of clinical variables. Obviously, prediction in daily clinical practice based on 1 biomarker result is more convenient than prediction based on the integration of three different variables. To appreciate the potential of a management strategy with hs-cTnT only, our data are put in clinical perspective in Figure 4, demonstrating 2 important implications. First, with a 100% sensitivity at 8 ng/L, we may be able to exclude extensive LGE in 50% of low to intermediate risk HC patients. Accordingly, in half of the patients one might consider not to perform LGE CMR imaging for risk stratification as no extensive LGE is expected to be found. Second, in the other half (hs-cTnT $\geq$8 ng/L) the pretest probability of finding extensive LGE has increased from 10% to 20%. As such, these data should be appreciated as the first evidence that corroborates with the previously suggested hypothesis that hs-cTnT may be used as a gateway to perform LGE CMR imaging.[7,8] Importantly, this example is intended to demonstrate potential future implications and is not meant to be implemented in clinical practice. Many institutions have adopted CMR imaging in their standard initial workup for patients with suspected HC, as CMR imaging may aid in the identification of hypertrophy that goes unnoticed on echocardiography. Moreover, LGE CMR imaging provides important information that may help differentiate between sarcomeric and nonsarcomeric causes of LV hypertrophy. Given these unique strengths of CMR imaging, it would not be sensible to, in general, waive CMR imaging based on a low hs-cTnT concentration. In contrast, in case there is little doubt concerning the diagnosis of HC, or in case of (relative) contraindications for LGE CMR imaging, hs-cTnT may provide valuable information on the (pretest) likelihood of extensive LGE.

Given the limited number of cases with LGE_{ext} and the moderate size of our study population, our findings warrant confirmation. Second, the definition of nonhigh SCD risk is not uniform, due to discrepancies between the AHA/ACC and ESC guidelines.[1,2] In this context, we performed an ancillary analysis based on the HC SCD risk-score[1] and demonstrated that hs-cTnT was independently predictive of extensive LGE in low to intermediate risk patients according to the ESC guidelines as well. With regard to extensive LGE, we acknowledge that it is not (yet) included in the guidelines, and that there is no consensus on the preferred method of LGE quantification. Where some advocate visual assessment, others use a signal-intensity-based cutoff, and we chose to use a semi-quantitative score.[19] In view of the

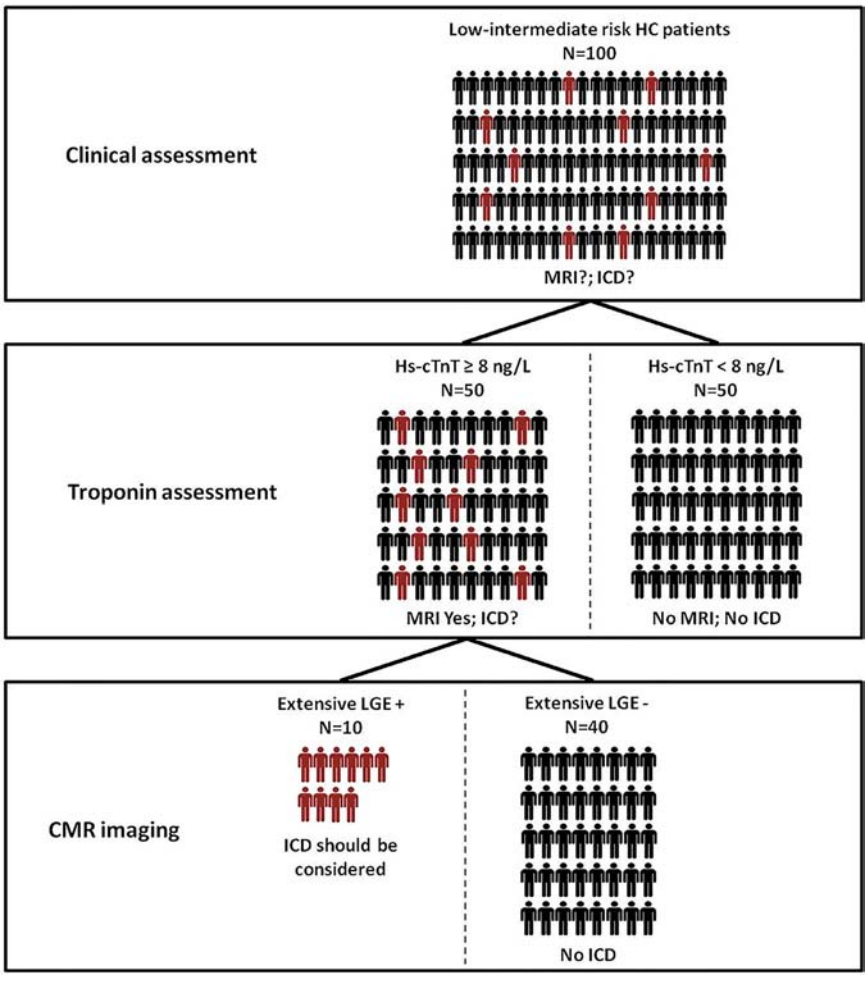

Figure 4. Potential management algorithm for low to intermediate risk HC patients.
This figure, *upper panel*, shows identification of low to intermediate risk HC patients using the conventional risk factors. Among these patients, about 10% will have extensive LGE (red). The *middle panel* demonstrates the stratification based on hs-cTnT. A hs-cTnT concentration <8 ng/L safely excludes extensive LGE. This represents half of our cohort. Moreover, in case of an hs-cTnT concentration ≥8 ng/L the chance of extensive LGE increased from 1 in 10 to 1 in 5 patients.
CMR = cardiovascular magnetic resonance; HC = hypertrophic cardiomyopathy; Hs-cTnT = cardiac troponin T assessed with a highly sensitive assay; LGE = late gadolinium enhancement. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

above, caution is warranted with regard to the use of a rigid cutoff. Our ancillary analyses with various cutoffs for extensive LGE demonstrated that hs-cTnT remained strongly associated with extensive LGE (Appendix B). Consequently, these results did not materially change our conclusions on the potential that hs-cTnT may have for future clinical risk stratification schemes in HC.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.04.020.

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